1. NAME OF THE MEDICINAL PRODUCT

NovoMix® 50 FlexPen®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of the suspension contains 100 units soluble insulin aspart*/protamine-crystallised insulin aspart* in the ratio 50/50 (equivalent to 3.5 mg). 1 pre-filled pen contains 3 ml equivalent to 300 units.

*Insulin aspart is produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

The suspension is cloudy, white and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NovoMix 50 is indicated for treatment of diabetes mellitus in adults.

4.2 Posology and method of administration

Posology

The potency of insulin analogues, including insulin aspart, is expressed in units, whereas the potency of human insulin is expressed in international units.

NovoMix 50 dosing is individual and determined in accordance with the needs of the patient. Blood glucose monitoring and insulin dose adjustments are recommended to achieve optimal glycaemic control.

The individual insulin requirement is usually between 0.5 and 1.0 unit/kg/day. NovoMix 50 may fully or partially meet this requirement.

In patients with type 2 diabetes, NovoMix 50 can be given as monotherapy or in combination with metformin when the blood glucose is inadequately controlled with metformin alone.

Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Special populations

In elderly patients (≥65 years old) and in patients with hepatic or renal impairment, glucose monitoring should be intensified and the insulin aspart dose adjusted on an individual basis.

Renal or hepatic impairment may reduce the patient's insulin requirements.

Paediatric population
The safety and efficacy of NovoMix 50 in children below 18 years of age have not been established. No data are available.

Transfer from other insulin medicinal products

Transfer to NovoMix 50 from other insulin preparations may require adjustment of dose and timing of administration. Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

NovoMix 50 is a biphasic suspension of the insulin analogue, insulin aspart.
The suspension contains rapid-acting and intermediate-acting insulin aspart in the ratio 50/50.

NovoMix 50 is for subcutaneous administration **only**.

NovoMix 50 is administered subcutaneously by injection in the thigh or in the abdominal wall. If convenient, the gluteal or deltoid region may be used. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see sections 4.4 and 4.8). The influence of different injection sites on the absorption of NovoMix 50 has not been investigated. The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

NovoMix 50 has a faster onset of action than biphasic human insulin and should generally be given immediately before a meal. When necessary, NovoMix 50 can be given soon after a meal.

For detailed user instructions, please refer to the package leaflet.

Administration with FlexPen
NovoMix 50 FlexPen is a pre-filled pen (colour-coded) designed to be used with NovoFine or NovoTwist needles. FlexPen delivers 1–60 units in increments of 1 unit. NovoMix 50 FlexPen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

NovoMix 50 must not be administered intravenously, as it may result in severe hypoglycaemia. Intramuscular administration should be avoided. NovoMix 50 is not to be

used in insulin infusion pumps.

Before travelling between different time zones, the patient should seek the doctor's advice since this may mean that the patient has to take the insulin and meals at different times.

Hyperglycaemia

Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis. Usually, the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. In case of hypoglycaemia or if hypoglycaemia is suspected, NovoMix must not be injected. After stabilisation of the patient's blood glucose, adjustment of the dose should be considered (see sections 4.2, 4.8 and 4.9).

Patients whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes.

Since NovoMix 50 should be administered in immediate relation to a meal, the rapid onset of action should be considered in patients with concomitant diseases or treatment where a delayed absorption of food might be expected.

Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirements. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.

When patients are transferred between different types of insulin medicinal products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin.

Transfer from other insulin medicinal products

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal insulin, human insulin or insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dose. Patients transferred to NovoMix 50 from another type of insulin may require an increased number of daily injections or a change in dose from that used with their usual insulin medicinal products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Injection site reactions

As with any insulin therapy, injection site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling and itching. Continuous rotation of the injection site within a given area reduces the risk of developing these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of NovoMix 50.

Skin and subcutaneous tissue disorders

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

Combination of NovoMix with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and NovoMix is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Avoidance of accidental mix-ups/medication errors

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between NovoMix and other insulin products.

Insulin antibodies

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to interact with the glucose metabolism.

The following substances may reduce the patient's insulin requirements:
Oral antidiabetic medicinal products, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulfonamides.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited clinical experience with NovoMix 50 in pregnancy.

Animal reproduction studies have not revealed any differences between insulin aspart and human insulin regarding embryotoxicity or teratogenicity.

In general, intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements return rapidly to pre-pregnancy levels.

Breast-feeding

There are no restrictions on treatment with NovoMix 50 during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the NovoMix 50 dose may need to be adjusted.

Fertility

Animal reproduction studies have not revealed any differences between insulin aspart and human insulin regarding fertility.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia while driving or operating a machine. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving or operating a machine should be considered in these circumstances.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions observed in patients using NovoMix are mainly due to the pharmacological effect of insulin aspart.

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see Description of selected adverse reactions below.

At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. These reactions are usually of a transitory nature.
Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Tabulated list of adverse reactions

The adverse reactions listed below are based on clinical trial data and classified according to MedDRA frequency and System Organ Class. Frequency categories are defined according to the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Immune system disorders	Uncommon – Urticaria, rash, eruptions
	Very rare – Anaphylactic reactions*
Metabolism and nutrition disorders	Very common – Hypoglycaemia*
Nervous system disorders	Rare – Peripheral neuropathy (painful neuropathy)
Eye disorders	Uncommon – Refraction disorders
	Uncommon – Diabetic retinopathy
Skin and subcutaneous tissue disorders	Uncommon – Lipodystrophy*
	Not known – Cutaneous amyloidosis*†
General disorders and administration site conditions	Uncommon – Oedema
	Uncommon – Injection site reactions

* see Description of selected adverse reactions
† ADR from postmarketing sources.

Description of selected adverse reactions

Anaphylactic reactions:
The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure) is very rare but can potentially be life-threatening.

Hypoglycaemia:
The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentrating, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

In clinical trials, the frequency of hypoglycaemia varied with patient population, dose regimens and level of glycaemic control. During clinical trials, the overall rates of

hypoglycaemia did not differ between patients treated with insulin aspart compared to human insulin.

Skin and subcutaneous tissue disorders:
Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

Paediatric population

The safety and efficacy of NovoMix 50 in children below 18 years of age have not been established. No data are available.

Other special populations

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

A specific overdose for insulin cannot be defined, however, hypoglycaemia may develop over sequential stages if too high doses relative to the patient's requirement are administered:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar-containing products.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting.
ATC code: A10AD05.

NovoMix 50 is a biphasic suspension of 50% soluble insulin aspart (rapid-acting human insulin analogue) and 50% protamine-crystallised insulin aspart (intermediate-acting human insulin analogue).

Mechanism of action and pharmacodynamic effects

The blood glucose lowering effect of insulin aspart is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

NovoMix 50 is a biphasic insulin, which contains 50% soluble insulin aspart.
This has a rapid onset of action, thus allowing it to be given closer to a meal (within zero to 10 minutes of the meal) when compared to soluble human insulin.
The crystalline phase (50%) consists of protamine-crystallised insulin aspart, which has an activity profile similar to that of human NPH insulin.

When NovoMix 50 is injected subcutaneously, the onset of action will occur within 10 to 20 minutes of injection. The maximum effect is exerted between 1 and 4 hours after injection. The duration of action is 14 to 24 hours (Figure 1).

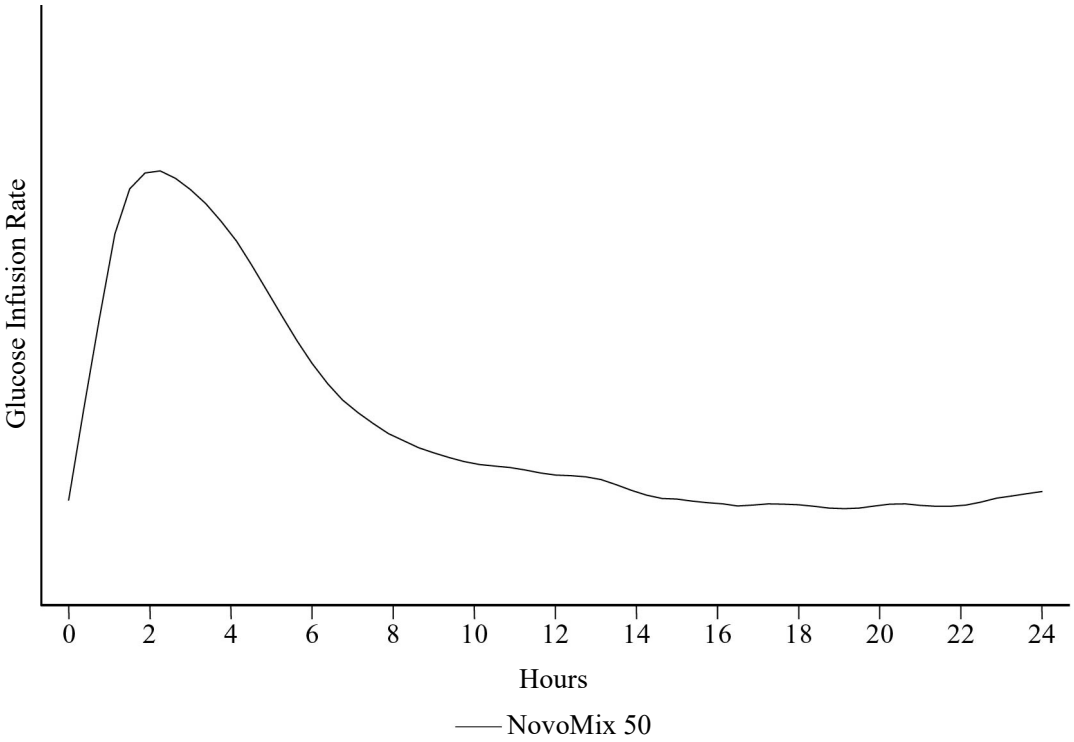

Figure 1: Activity Profile for NovoMix 50 in Healthy Caucasian Subjects.

Insulin aspart is equipotent to human insulin on a molar basis.

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

In insulin aspart, substitution of amino acid proline with aspartic acid at position B28 reduces the tendency to form hexamers as observed with soluble human insulin.
The insulin aspart in the soluble phase of NovoMix 50 comprises 50% of the total insulin; this

is absorbed more rapidly from the subcutaneous layer than the soluble insulin component of biphasic human insulin. The remaining 50% is in crystalline form as protamine-crystallised insulin aspart; this has a prolonged absorption profile similar to human NPH insulin.

In healthy volunteers, a mean maximum serum concentration of 445 ± 135 pmol/l was reached about 60 minutes after a subcutaneous dose of 0.30 unit/kg body weight. In type 2 patients with diabetes, the maximum concentration was reached about 95 minutes after dosing.

Special populations

The pharmacokinetics of NovoMix 50 have not been investigated in paediatrics, elderly patients or in patients with renal or hepatic impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

In *in vitro* tests, including binding to insulin and IGF-1 receptor sites and effects on cell growth, insulin aspart behaved in a manner that closely resembled human insulin. Studies also demonstrate that the dissociation of binding to the insulin receptor of insulin aspart is equivalent to human insulin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Sodium hydroxide (for pH adjustment)
Metacresol
Hydrochloric acid (for pH adjustment)
Phenol
Disodium phosphate dihydrate
Sodium chloride
Protamine sulfate
Zinc
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
<u>During use or when carried as a spare:</u> The product can be stored for a maximum of 4 weeks.

6.4 Special precautions for storage

<u>Before opening:</u> Store in a refrigerator (2°C–8°C). Keep away from the cooling element. Do

not freeze.

During use or when carried as a spare: Store below 30°C. Do not refrigerate.
Do not freeze. Keep the cap on FlexPen in order to protect it from light.

6.5 Nature and contents of container

3 ml suspension in cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene. The cartridge contains a glass ball to facilitate resuspension.

Pack size of 5 pre-filled pens.

6.6 Special precautions for disposal and other handling

After removing NovoMix 50 FlexPen from the refrigerator, it is recommended to allow NovoMix 50 FlexPen to reach room temperature before resuspending the insulin as instructed for first time use.

Do not use this medicinal product if you notice that the resuspended liquid is not uniformly white, cloudy and aqueous.
The necessity of resuspending the NovoMix 50 suspension immediately before use is to be stressed to the patient.

NovoMix 50 which has been frozen must not be used.

The patient should be advised to discard the needle after each injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Needles and pre-filled pens must not be shared.

7. LICENSE HOLDER

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8. MANUFACTURER

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138-75-31773

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